Declaration of Dr. Steven Craig Novick

Qualifications of Dr. Novick

1. I, Dr. Steven Craig Novick, received a medical doctor degree from New York University School of Medicine in 1995. I received a doctorate degree in Molecular Oncology in 1994 from the same University. I have published numerous articles relating to various cancers and the use of certain therapies in the treatment of different cancers.

2. Since 2004, I have been serving as the Medical Director for Genta Incorporated. During this time I have assisted in the preparation of NDA filings for submission to the FDA to seek marketing approval for Genasense®. I assisted in the analysis and presentation of safety and efficacy data for Genasense. Genasense is a bcl-2 antisense oligonucleotide, also referred to as G3139.

Genasense Background and General Comments

3. Before the priority date of the '170 application (August 25, 2000), the generally accepted course of therapy was a 14-day treatment regimen. See chart attached at Tab A.

4. Not until after the present inventor's discovery that a shorter cycle of therapy would be useful in treating cancer, did others move to a shorter cycle of therapy. See chart at Tab B.

5. The first paper to discuss the use of a shorter treatment regimen (published after the filing date of the '170 application) was the Jansen et al. paper, Lancet, Vol. 356, pp. 17281733, (Nov. 18, 2000), which reports research sponsored by Genta. This paper shows efficacy in 14 patients where the patients received increased doses of BCL-2 antisense oligomer for a five-day cycle of therapy.

Summary of Conclusions: there is no teaching or suggestion in Webb and Waters to shorten the treatment regimen to less than a 2-week course of therapy

6. I have read and understood the subject application, U.S. 09/709,170 ("the '170 application").

7. I have also read the Office Action issued by the USPTO on November 28, 2006 and the two references referred to therein (Webb et al., The Lancet, 1997 Vol. 349; 1137-1141 ("Webb")) and Waters et al., Journal of Clinical Oncology, 2000 Vol. 18:1812-1823 ("Waters")).

8. I have concluded that one skilled in the art would not be motivated by the teachings of Webb and Waters to reduce the usual course of therapy for bcl-2 from a two week course of therapy to a three to nine day course of therapy, as presently claimed in the '170 patent.

9. The results reported in Webb and Waters are not impressive, and therefore, one skilled in the art reviewing these references would not be motivated to provide a shorter course of therapy, especially since most of all of the patients in the studies did not respond satisfactorily, despite 14 days of treatment. Those skilled in the art that develop drugs and treatment regimens do not routinely shorten cycles of therapy. To be motivated to do so (and to go against accepted treatment schedules) would require convincing results, which simply are not reported in Webb and Waters.

Webb Reference: no motivation to shorten the course of therapy

10. After reading the Webb reference, it is my opinion that this reference teaches a two-week treatment regimen. *See* Webb, p. 1137 left column: "A daily subcutaneous infusion of 18-base, fully phosphorothioated antisense oligonucleotide **was administered for 2 weeks** to nine patients. . . ." (emphasis added); *see also* page 1138, left column "**One 2-week course of treatment** was given. Patients were followed for 4 weeks after the end of treatment. If there was evidence of tumor response, a second course was considered." (emphasis added). Thus, in my opinion, one skilled in the art would read Webb as teaching a two-week course of therapy.

11. In my opinion, the mere fact that the authors in Webb report the bcl-2 levels of one patient (patient number 6) measured at week 1 and week 2 during the course of the two week course of treatment does not teach or suggest to one skilled in the art to treat a patient for cancer by shorting the regimen to less than the two week course of treatment, let alone shorten the course of treatment to a cycle of therapy consisting of three to nine days (as is presently claimed in the '170 application).

12. In my opinion, the mere fact that one patient (patient 6) at day 7 had reduced levels of BCL-2, does not provide evidence of treatment or a response, nor motivation to shorten the treatment regimen. One would not know whether the total infusion of 14 days was necessary to provide treatment of cancer or whether infusion of 7 days of therapy would be sufficient. This is especially the case, since the patient 6 did not show a promising cancer response.

13. One skilled in the art would understand that bcl-2 levels would in fact most likely go down with bcl-2 antisense treatment but would not know based on Webb's study whether this reduction represented a transient reduction or a stable reduction of bcl-2 levels. Further, one skilled in the art reading Webb would not know if this reduction of bcl-2 levels would likely treat cancer, especially if the bcl-2 reduction was transient.

14. In my opinion, one skilled in the art reading Webb would <u>not</u> be motivated to shorten the course of therapy, but rather would be motivated to continue with a longer course of therapy, or change the regimen to a course of therapy with a higher dose, or add to the regimen a second, third, or fourth (or more), course of therapy, or a combination of all of these changes to the regimen. In my opinion, by no means would one be motivated to shorten the course of therapy to treat cancer just because one patient showed reduced bcl-2 levels at week 1 and week 2, especially since patient 6 only showed a partial or negligible tumor response (page 2, column 1139).

15. Thus, it is my opinion that Webb does not teach or suggest changing the treatment regimen to anything shorter than a two-week course of therapy, let alone to a three to nine day course of therapy as presently claimed in the '170 application.

Waters reference: no motivation to shorten the course of therapy

16. After reviewing Waters, I conclude that this reference also teaches a course of therapy for two weeks. *See* Page 1812, first column: "Twenty-one patents with Bcl-2-positive relapsed NHL **received a 14-day subcutaneous infusion** of G3139. . ."(emphasis added); *see also* page 1813, left column: "Antisense oligonucleotide G3139 was delivered as a continuous subcutaneous infusion for **14 days** by a portable infusion pump. Toxicity was graded according to the common toxicity criteria and assessed **during the 2-week treatment period** and during the subsequent 4 weeks. One course of treatment was planned per patient, but additional courses of treatment were considered in the **event of a tumor response**." (emphasis added).

17. Because the purpose of this study was to determine safety ("These objectives provided the rationale for a phase I trial of antisense oligonucleotide G3139" page 1813, first col.), the authors studied and reported toxic events and noted that in certain patients, the treatment with bcl-2 antisense oligonucleotide was discontinued before completing the full 2-week course of therapy. See page 1815, col. 2. However, it is my opinion that stopping treatment during a course of therapy due to adverse events, does not teach or suggest using a shorter course of therapy to treat cancer.

18. Waters reports that certain patients had adverse effects and had their course of therapy terminated. For example, Patient 15's treatment was discontinued on day one, Patient 16's treatment was discontinued on day 12 and Patient 17's treatment was discontinued after day 2 (48 hours). *See* page 1815, col. 2. Thus, even if one skilled in the art would be motivated to shorten the cycle of therapy to treat cancer, there is nothing in this data to teach or suggest shortening the cycle of therapy to three to nine days, separated by an interval of time when the therapy is not given and repeating with another three to nine day cycle of therapy (as the current pending claim requires.)

19. Even if one were to read Waters as teaching Patient 17 only receiving 2 days of treatment followed by another course of therapy (since Waters reports that patient 17 received a second course of therapy), Waters still does not teach or suggest the claimed method of treating cancer where the patient is given a course of therapy of three to nine days, followed by a rest period, followed by another three to nine day course of therapy. First, patient 17 only received

two days of therapy as Waters states that treatment was discontinued after 48 hours because of dose limiting toxicity. Second, there is nothing to teach or suggest that Patient 17's second course of therapy at a lower dose was anything but the planned 14-day cycle required by the protocol. The discussion of Patient 17 therefore does not suggest the claimed invention, wherein multiple cycles of therapy each consist of three to nine days.

20. Waters reports that Patient 18's treatment was discontinued at day 8. However, there is nothing in article that states that Patient 18 went on to receive a second course of therapy. Waters mentions that only three patients (Patient 2, 17 and 21) received a second course of therapy. Waters but does not teach or suggest that it was Patient 18 and in fact clearly indicates by deduction that it was not Patient 18. *See* page 1813, first col. and page 1818, first col. Thus, there is no teaching or suggestion to shorten the course of therapy from 14 days to three to nine days and then continue on with another course of therapy of three to nine days after a rest period between.

21. In my opinion, even Waters was not impressed with the results of the study and therefore did not contemplate a shorter treatment regimen, but instead proposed a combination therapy. On page 1821, Waters notes that "[o]ne of the most interesting possibilities is their use as chemosensitizing agents . . . ." On page 1822, Waters further notes that "based on the results from this phase I study, a phase II trial is now in progress at Royal Marsden Hospital using G3139 in combination with standard cytotoxic regimens . . . " Thus, even Waters does not teach or suggest the use of a shorter treatment regimen, but rather suggest using BCL-2 in combination with cytotoxic reagents.

22. I, therefore, conclude that Waters does not teach or suggest a cycle of therapy to treat cancer consisting of three to nine days, followed by an interval of time where no bcl-2 antisense oligonucleotide is administered, followed by another three to nine day cycle of therapy (as required by the claims of the '170 application).

Conclusion

23. In addition to having no teaching or suggestion in Webb or Waters, it is my opinion, that one skilled in the art, reading Webb and Waters, would not have been motivated to treat cancer by shortening the cycle of therapy to from the accepted 2 week cycle of therapy to a cycle of therapy consisting of three to nine days, followed by an interval of time where no bcl-2 antisense oligonucleotide is administered, followed by another three to nine day cycle of therapy.

24. All statements made herein of my own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001, and may jeopardize the validity of the application or any patent issuing thereon.

4/25/07
Date

Dr. Steven Craig Novick